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(54) Title: IMPLANT DEVICE AND METHOD FOR TREATMENT OF GLAUCOMA			
(57) Abstract An implant device for use in the treatment of glaucoma or intraocular pressure in an eye of a patient, comprises a hollow fibre, preferably of a biologically inert material which is microperforated in the walls thereof. In use, the device is implanted into the eye so as to extend between the anterior chamber of the eye and the periocular tissues.			

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IMPLANT DEVICE AND METHOD FOR TREATMENT OF GLAUCOMA

5 Field of the Invention

This invention relates to the treatment of glaucoma or intraocular pressure, and in particular it relates to an implant device and method for carrying out this treatment.

10 Background to the Invention

In the USA over two million people suffer from glaucoma. The disease is a major cause of blindness, with approximately 30% of patients having visual impairment and 3.5% classified as legally blind (1). In Australia it is estimated that 120,000 people suffer from glaucoma, and it represents the fourth leading cause 15 of people registering for the blind pension (2). Current treatments are unsatisfactory: topical drug treatment is not without side effects and is required for life, and surgical intervention is frequently unsuccessful.

The most prominent aspect of glaucoma is raised pressure inside the eye 20 which is associated with the loss of nerve fibres in the retina, and partial or total loss of vision is a consistent sequel to this primary pathology. The intraocular pressure (IOP) at which irreversible damage to the optic nerve occurs is quite variable between individuals, however the one common factor is that all patients with glaucoma benefit from reduction of their IOP. All current primary therapies 25 are directed at reducing the intraocular pressure to below 15 mmHg, a level at which retinal damage is minimised.

Raised intraocular pressure is currently treated pharmacologically and 30 surgically. IOP is determined by the rate of production in the eye and the rate of outflow from the eye of an optically transparent nutrient fluid called aqueous. Therapy is aimed at either reducing aqueous production, or increasing the rate of outflow of aqueous from the eye.

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Aqueous is a nutrient fluid of exquisite optical properties which contains, amongst others, 25 times the serum concentration of ascorbic acid, 3 times the serum concentration of lactate, as well as glucose, oxygen and a unique spectrum of amino acid concentrations (3). Because of this unique nature of aqueous, the 5 preferred method of effecting change in the hypertensive eye is to increase the outflow of aqueous rather than reducing the rate of renewal.

Increasing the outflow of aqueous can be achieved pharmacologically with topical (or oral) agents that cause the ciliary muscle to increase tone causing the 10 trabecular mesh to become more porous. These agents have many disadvantages, not the least of which is miosis which can be quite debilitating in patients with reduced retinal function. For this reason, and others, these agents are not the usual first line of therapy for primary open angle glaucoma (POAG).

15 Topical medications have a number of disadvantages. They may not be available to many patients (worldwide) due to expense or availability, and when prescribed there is a reported up to 30% compliance failure rate. The medications have significant short and long term side effects on the eyes and tend to have reducing efficacy over time. In addition some patients may experience significant 20 systemic side effects from the medication. Topical medication may not be as effective as preventing glaucoma damage as surgery (3).

Laser surgery (Laser trabeculoplasty) has limited application in some types of glaucoma, but its wide application has given disappointing results.

25

Surgical intervention (trabeculectomy) to increase the facility of outflow of aqueous is achieved by creating an alternate pathway from the anterior chamber to the periocular tissues. Various surgical strategies over 80 years led to the development of the current trabeculectomy operation, which Sugar first described 30 in 1961 (4). Despite it's long incubation period, the current operation is imperfect and is not frequently adopted as first line therapy.

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In addition to surgical failures, trabeculectomy has a high rate of post-operative complications: in one prospective study up to 40% of treated eyes suffered one of the following complications: hyphaema, transient flat anterior chamber, choroidal detachment or iritis with synechiae formation (5). This study 5 also found that some 40% of eyes post-trabeculectomy developed significant changes in the lens, and 3/4 eyes suffering from prolonged hypotony developed cataract. These results compare to previous retrospective studies (6).

Renewed interest in surgery as first line therapy has been encouraged by 10 a recent publication from Glasgow in which 99 patients with Primary Open Angled Glaucoma (POAG) were prospectively randomised to receive either surgical or medical treatment. At five years, this study has provided the challenging observation that surgical intervention (trabeculectomy) provided more stable control and less field loss than medical therapy, even when combined with later 15 trabeculectomy (7).

The concept of treating glaucoma with an implant arose from basic surgical principles of drainage of a cavity. The most popular recent implant, the Molteno Implant, is a comparatively large and complicated silicone structure (8). Particular 20 skill is required for its successful implantation and it is responsible for a number of unwanted side-effects.

In general, current implants are bulky, complicated to place satisfactorily, and have the risk of displacement and erosion (9,10,11). Reoperation is difficult. 25 Post-operative hypotony and shallow anterior chamber are common in implant surgery (15-45%) and appear to be related to choroidal effusion (7,12). Recently the Molteno implant has been shown to cause declining endothelial counts with increased pleomorphism and polymegathism (13). Operative modifications intended to bypass some of these problems tend to be complicated and require 30 further intervention postoperatively to implement free drainage of aqueous.

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Although surgery may be desirable as first line therapy two major problems exist with all current surgical treatments:

1. the outflow pathway scleroses, and the pathway may become non-
5 patent, and
2. the quantity of outflow is not able to be regulated easily

The combination of prolonged antiglaucomatous medication and significant anterior segment operative trauma sabotages attempts at creating a permanent 10 lowering of IOP. A single operation is preferable to lifelong administration of medication, even in countries where the latter is an option. Current trabeculectomy operations are unsatisfactory for third world environments as the amount of post-operative care required is prohibitive. Furthermore, certain racial groups have a higher rate of failure related to an increased propensity to scarring. 15 Thus early surgery which maintains lowered IOP before prolonged medical therapy or visual loss, in which there is minimal disturbance of the anterior chamber and surrounding tissues, and which has low post-operative risk, is seen as a major goal in the treatment of glaucoma.

20 It is a primary object of the present invention to provide a method for the surgical treatment of glaucoma by reduction of intraocular pressure using a novel implant, which method is safe, reliable and simple.

Summary of the Invention

25 In accordance with the present invention there is provided an implant device for use in the treatment of glaucoma or intraocular pressure in an eye of a patient, which comprises a hollow fibre, preferably of a biologically inert material, said fibre being microperforated in the walls thereof and being adapted on implantation into the eye of a patient to extend between the anterior chamber of the eye and the 30 periocular tissues, particularly the subconjunctival space of the eye.

It is to be understood that whilst the device of the present method is principally intended for use in the treatment of a human patient, it is equally applicable for use in the treatment of non-human animals such as companion animals (dogs and cats), horses (particularly race horses), and the like.

5

Preferably, the implant device of this invention is implanted into the eye so as to provide a direct path into the eye with one end of the fibre located in the anterior chamber. In this preferred embodiment, the end of the fibre which is to extend into the anterior chamber may be provided with anchoring means, such as

10 a flange, T-shaped fitting of the microperforated tubing, silicon tubing or the like, to hold that end of the fibre in place in the anterior chamber. If desired, the other end of the fibre which is to extend into the subconjunctival space or other periocular tissues may also be provided with similar anchoring means to hold that end in the subconjunctival tissues. In an alternative arrangement, however, the

15 device may be implanted as a suture, with the fibre forming a loop in the anterior chamber and the two free ends located beneath the conjunctiva of the eye.

Preferably also, the surface of the microperforated device of this invention, is modified, in particular by treatment with heparin, in order to increase its

20 biocompatibility, in particular to reduce fibroblast proliferation. Suitable treatment processes, including covalent binding of heparin to solid surfaces, are well known in the art.

Suitable hollow fibres for use as an implant device in accordance with this

25 invention are, for example, fibres having an external diameter of about 500-600 μm and an internal diameter of about 200-350 μm . The fibres suitably have a pore size larger than 0.2 μm , and preferably the pore size is 0.4 - 0.6 μm or larger. The hollow fibres may, for example, be made of polypropylene or a similar biologically inert material. Particularly preferred microperforated hollow fibres are

30 polypropylene fibres having an average pore size of 0.4 μm .

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- In a modification of the device of this invention as broadly described above, the lumen of the hollow fibre of the implant device may be at least partially occluded with a biodegradable material, such as a biodegradable polymer. Suitable biodegradable polymers include those that will degrade rapidly and
- 5 produce little reactive (scarring) byproducts. They include, for example, the polyglycolic and polylactic acid polymers and mixtures thereof (such as 50:50 mixtures) which already have intraocular use, as well as gelatin, or polyanhydrides or polyphosphates, (although these latter varieties may be too slow in degradation). Such occlusion may be achieved by coating the inside walls of the
- 10 fibre, or in fact filling the lumen of the fibre, with the biodegradable material. Alternatively, the biodegradable material may be coated on the outside of the fibre. If desired, the biodegradable material may also include pharmacologically active agents, such as drugs for reducing scarring, steroids such as dexamethasone or hydrophobic forms thereof, non-steroidal anti-inflammatory agents, or
- 15 antimetabolite agents such as mitomycin C 5-fluorouracil or adriamycin. Such an occluded fibre may be used to prevent the eye becoming too soft immediately after implantation, and to act as a slow release reservoir of the pharmacologically active compounds.
- 20 In another aspect, the present invention provides a method for treatment of glaucoma or intraocular pressure in an eye of a patient, which comprises the step of implantation into said eye of an implant device as broadly described above, said device on implantation extending between the anterior chamber of the eye and the periocular tissues, particularly the subconjunctival space of the eye.
- 25
- As described above, the patient may be either a human or animal.
- Detailed Description of the Invention**
- One of the major difficulties experienced in treatment of glaucoma using
- 30 implants has been the biological response of the tissues; in essence the eye is always trying to plug holes that are made in it. It can do this by one or both of two ways. The first is probably the method that causes the glaucoma in the first

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place (ie gradual obstruction of the outflow passages from the eye), and the second is the healing response.

The second mechanism, that of wound healing and fibrosis, is of vital

5 importance, and it is this which is the primary determinant of the long term success of the operation. Many methods of reducing or retarding the fibrosis have been tried, however they all rely of creating a large wound, and hence a large biological stimulus to healing and fibrosis. The essence of the present invention is to minimise the trauma, use an implant made of a biologically inert material, and
10 preferably to coat the surface of the implant in heparin, a molecule that is found lining the surface of all blood vessels, so that the implant disrupts the tissues minimally, and is so designed and treated that any subsequent fibrotic reaction is minimalised.

15 Microperforated fibres are currently used in a great variety of applications and hence are readily available. By way of example, such fibres are used in plasmapheresis filters for use in human blood filtration where they are used grouped together in bundles of 2000. They provide a very high surface area to volume ratio for diffusion of fluids through their walls, and are biologically inert.

20 Suitable fibres may however be available from other sources, or they may be made especially for the implant device of this invention. By implanting one of these individual fibres through the wall of the eye in accordance with the present invention, there is provided a stable and permanent route for drainage of fluid from the eye.

25

The implant of this invention is designed to be simple, quick to place under local anaesthesia, and have minimal post-operative care. These are advantages in any community, but are necessities in the third world where glaucoma remains essentially untreated.

30

1. **Ease of Placement:**

Preferably, the implant device of this invention is placed with one end of the fibre in the anterior chamber of the eye and the other outside the eye in the subconjunctival space. The fibre is implanted as a sheath around a stilette-type

5 needle, and the needle then withdrawn leaving the fibre in place with one end anchored in the anterior chamber and providing a water tight seal around the outside of the fibre where it passes through the wall of the eye. The conjunctiva is lifted forward with atraumatic tissue forceps and the free end of the fibre located in the subconjunctival space before the conjunctiva is allowed to return to its
10 normal anatomy leaving the free end buried beneath the conjunctiva. Alternatively, the device may be placed from the inside of the anterior chamber, so that the fibre enters the subconjunctival space after being passed through the wall of the eye.

Alternatively, the device may be implanted as a suture. The fibre will be
15 swaged to a cutting needle of approximately 8-10 mm diameter. The fibre will be introduced to the anterior chamber as a suture and passed through the limbal tissue. Conjunctiva will be grasped some 15 mm posterior to the limbus and brought forward with atraumatic tissue forceps. The tented conjunctiva will be perforated by the needle as it enters the eye. When the tip of the needle is
20 delivered the fibre is pulled through, such that the middle of the fibre remains in the anterior chamber. The needle can then be cut off, the conjunctiva relaxed, and the two free ends can be sutured to the sclera 15 mm posterior to the limbus. The fibre now lies with a loop in the anterior chamber and two free ends buried beneath the conjunctiva with minimal trauma to the periocular tissues.

25

2. **Blockage of the Implant:**

(a) From within the anterior chambers: aqueous is known to obstruct microporous filters of pore diameter 0.2 μm (14). The reason for this action of aqueous is unclear, and has only recently been demonstrated. The action is due
30 to the combined actions of a protein and non-protein components of the aqueous, and is not due to fibrin/fibrinogen (15). Fibre pore diameter would need to be larger than 0.2 μm to assure continued patency of the intraocular portion of the

fibre. Fibres obtained for the initial study have a pore size of 0.5-0.6 μm (gambro[®] PF2000, plasmapheresis fibres). If studies show blockage, then fibres can be especially made with pore sizes larger.

- 5 (b) In the subconjunctival space: The clinical problem of fibrosis of outflow tracts led to the laboratory observation that aqueous from glaucomatous eyes supported proliferation of fibroblasts in culture, and that aqueous from normotensive eyes did not. A similar aqueous state was induced in a normal eye by operation on the anterior segment. It is not possible to induce "nutrient" 10 aqueous with simple anterior chamber aspiration in monkeys, nor by subconjunctival biopsy, but trabeculectomy is sufficient to induce changes in the aqueous (16). Although it is difficult to prove a pathogenic role of aqueous in glaucoma, it is likely to have a significant effect on the results of surgery (16,17). A later study has shown that long term topical antiglaucomatous medication results 15 in significantly increased number of macrophages, lymphocytes, mast cells and fibroblasts in the conjunctiva and tenon's capsule of recipients (18).

- Fibrin/fibrinogen has been identified in the subconjunctival tissue of non-human primates 2-7 days post-trabeculectomy (19). Leakage of plasma from 20 damaged blood vessels causes the formation of an extravascular clot consisting of fibrin, fibrinogen, fibronectin and platelets (20). This serves as a scaffold for the migration of inflammatory cells. Experiments suggest that the quantity of fibrin scaffold present in a wound determines the amount of scar tissue that ultimately develops (21). Furthermore, aqueous has been shown to accelerate clotting time, 25 as a result of a procoagulant action (22).

- Heparin is well known for its actions in prevention of the clotting cascade, however it has also been demonstrated to have an action directly against fibroblast proliferation, and specifically against sclera fibroblasts (23). It has also been 30 demonstrated that heparin bound to polymer surfaces prevents the normal adherence and proliferation of human sclera fibroblasts over that surface (24).

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3. Regulation of Outflow:

Current surgical intervention in the treatment of glaucoma involves two parts: firstly, the creation of an outflow pathway (sclerostomy) from the eye; and secondly, the establishment of a tissue bed for the absorption of aqueous drained

5 from the eye.

The size of the sclerostomy required can be calculated from Poiseuille's equation as the fluid flow is known (2.5 μ l/min), the path length is normally under 2 mm, and the driving pressure needs to be as low as possible (under 2 mm/Hg).

10 From this it can be ascertained that the sclerostomy diameter need only be greater than 200 μ m diameter to not impede fluid flow from the eye. The longer path length required in the use of the implant device of the present invention may necessitate the use of a fibre of larger diameter, for example, up to 350 μ m.

15 The small size of the fibre lumen should be adequate to handle a proportion of aqueous outflow, the rest being catered for by uveoscleral and remaining flow through the trabecular meshwork. Aqueous production has been determined at 2.5 μ l/min (25).

20 Given that the diameter of the tube is not a limiting factor in the outflow, it is the resistance of the fluid entering the subconjunctival space that is important. Microperforated tubes offer the advantage that the whole of the wall of the tube acts as a diffusion surface. Given a subconjunctival length of 10mm, and hence a total length of 20 mm, the surface area of a tube of outside diameter is 25 approximately 20 mm². This is comparable to the original plate surface area as specified by Molteno (8).

30 Aqueous normally flows from the eye through dedicated channels. Surgical procedures allow aqueous to be absorbed as tissue oedema (the "bleb"). Aqueous is virtually protein free (in the non-inflamed eye) and is thus drawn across the capillary walls by oncotic pressure. Scarring of the subconjunctival space,

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reduction in volume or capillarity of the absorptive tissue, or changes in the characteristics of aqueous will all jeopardise or prevent absorption.

Failure of aqueous to exit the eye ("failure of the sclerostomy") or to be absorbed at adequate rate from the subconjunctival tissue ("failure of the bleb") will result in failure of the operation to lower the pressure in the eye. Most operations for glaucoma fail because of scarring causing "failure of the bleb".

Optimally, drainage of aqueous is achieved atraumatically and is hydrodynamically stable early and in the long term. All current surgeries require extensive manipulation of ocular and periocular tissues and involve relatively prolonged periods of instability in the outflow dynamics. These are the major contributors to the high rate of side effects of the current procedures. Regulated outflow in accordance with the present invention reduces the risk of postoperative hypotony and it's associated complications.

Resistance to flow across the wall of the implant device of this invention adds another dimension to the regulation of the outflow of aqueous from the eye.

Further features of the implant device of the present invention and of its use in the treatment of glaucoma will be apparent from the following non-limiting Example.

EXAMPLE 1

25

The fibres used in the initial trial were microperforated polypropylene fibre, manufactured by Gambro having an average pore size 0.4 μm , with a surface modification in which the fibres were coated with heparin according to a protocol described by Larm et al (26).

30

The preferred animal model is the rabbit and has been used in many animal trials of glaucoma implants (27,28). It has a relatively large eye, docile personality,

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and reacts well to anaesthesia. It has ocular anatomy not dissimilar to the human, and an IOP in the same range, although it should be noted that the rabbit is well known to have a high propensity to scarring in the subconjunctival space.

5 As an initial trial ten animals were entered. The experiment was designed to run for three months from the time of implantation.

Measurements of intraocular pressure were made every week for the duration under topical anaesthesia using a Schiotz indentation tonometer with a 10 7.5 g weight. New Zealand white (NZW) rabbits are known to have an extensive diurnal fluctuation in IOP (29), and every effort was made to ensure consistency of testing procedure and time.

15 Fibres were implanted under general anaesthesia using a stilette-type needle as previously described. Fibres were passed from the conjunctival space through the limbal sclera such that the end remained buried under the conjunctiva and the anterior end was located in the anterior chamber in the angle. No sutures or glue were used on the conjunctiva.

20 The results are displayed in Figure 1A as the unadjusted Schiotz readings as no reliable conversion scale exists. The higher the reading the lower the intraocular pressure. Treated rabbit eyes are displayed with the unbroken lines, and the untreated eyes with hatched lines. The experiment was continued for 12 weeks.

25

The results indicate that a total of 10 NZW rabbits were entered. One treated eye failed after the first week. Clinically it was clear as to the reason, and in the context of this experiment should not be regarded as a failure. A significant difference in pressures was noted at the 12 week interval.

30

Figure 1B is a summary of the Schiotz pressure difference between the treated and untreated eyes as shown in Figure 1A.

EXAMPLE 2

In a second experiment 24 NZW rabbits were entered. One eye at random was selected for implantation with a heparin coated polypropylene hollow 5 microperforated fibre of wall pore size average 0.4 μm manufactured by Memtec (Aust.). The experiment ran for three months and the IOP was measured weekly with a Tonopen[®]. Unlike the tonometer of Example 1, this machine measures IOP, although the machine is calibrated for humans and the eye wall resistance of the rabbit is lower, and thus the machine might be expected to under-read.

10

The results are shown in Figures 2A and 2B, and it can be seen that a difference in pressure between the treated and untreated eyes exists to the termination of the experiment.

15

The above Examples are included for the purposes only of illustration of the present invention. It will be appreciated that many variations may be made without departing from the spirit and scope of the invention as broadly described herein.

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CLAIMS:

1. An implant device for use in the treatment of glaucoma or intraocular pressure in an eye of a patient, which comprises a hollow fibre, said fibre being microperforated in the walls thereof and being adapted on implantation into the eye of the patient to extend between the anterior chamber of the eye and the periocular tissues.
2. An implant device according to claim 1, wherein said hollow fibre is of a biologically inert material.
3. An implant device according to claim 1 or claim 2, wherein one end of the fibre extends into the anterior chamber of the eye and is provided with anchoring means to hold said one end of the fibre in place in the anterior chamber.
4. An implant device according to claim 3, wherein the other end of the fibre extends into the subconjunctival space of the eye and is provided with anchoring means to hold said other end of the fibre in place in the subconjunctival space.
5. An implant device according to claim 1 or claim 2, wherein said fibre forms a loop extending through the anterior chamber with the two ends of the fibre located in the subconjunctival space.
6. An implant device according to any of claims 1 to 5, wherein the surface of the fibre is modified to increase the biocompatibility thereof.
7. An implant device according to claim 6, wherein said surface modification comprises treatment with heparin.
8. An implant device according to any of claims 1 to 7, wherein said fibre is a microperforated, hollow polypropylene fibre.

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9. An implant device according to claim 8, wherein said fibre has an external diameter of about 500-600 μm , an internal diameter of about 200-350 μm , and a pore size of at least 0.2 μm , preferably at least 0.4-0.6 μm .
10. An implant device according to any of claims 1 to 9 wherein the lumen of said hollow fibre is occluded with a biodegradable polymer or other biodegradable material.
11. An implant device according to claim 10 or claim 11, wherein said biodegradable polymer is selected from polyglycolic acid polymers, polylactic acid polymers, polyglycolic/polylactic acid copolymers, and gelatin.
12. An implant device according to claim 10 or claim 11, wherein said biodegradable material includes a pharmacologically active agent.
13. An implant device according to claim 12, wherein said pharmacologically active agent is selected from drugs for reducing scarring, steroid or non-steroidal antiinflammatory agents and antimetabolic agents.
14. A method for the treatment of glaucoma or intraocular pressure in an eye of a patient, which comprises the step of implantation into said eye of an implant device according to any of claims 1 to 13, said device on implantation extending between the anterior chamber of the eye and the periocular tissues.
15. A method according to claim 14, wherein the patient is a human.
16. A method according to claim 14, wherein the patient is a non-human animal.
17. The use of an implant device according to any of claims 1 to 13 in the treatment of glaucoma or intraocular pressure in an eye of a patient.

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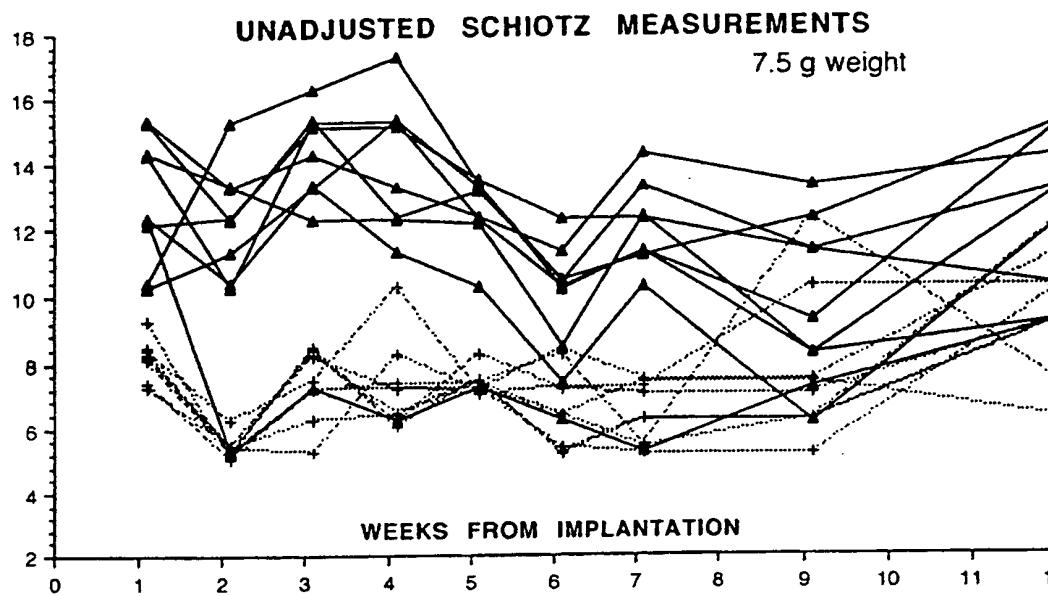


FIGURE 1A

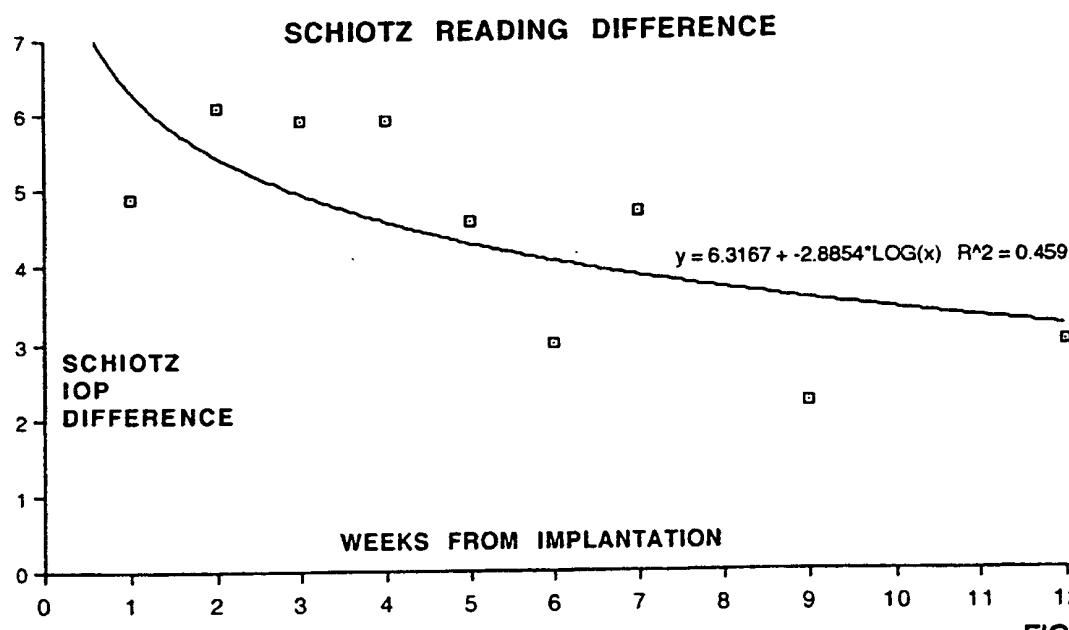
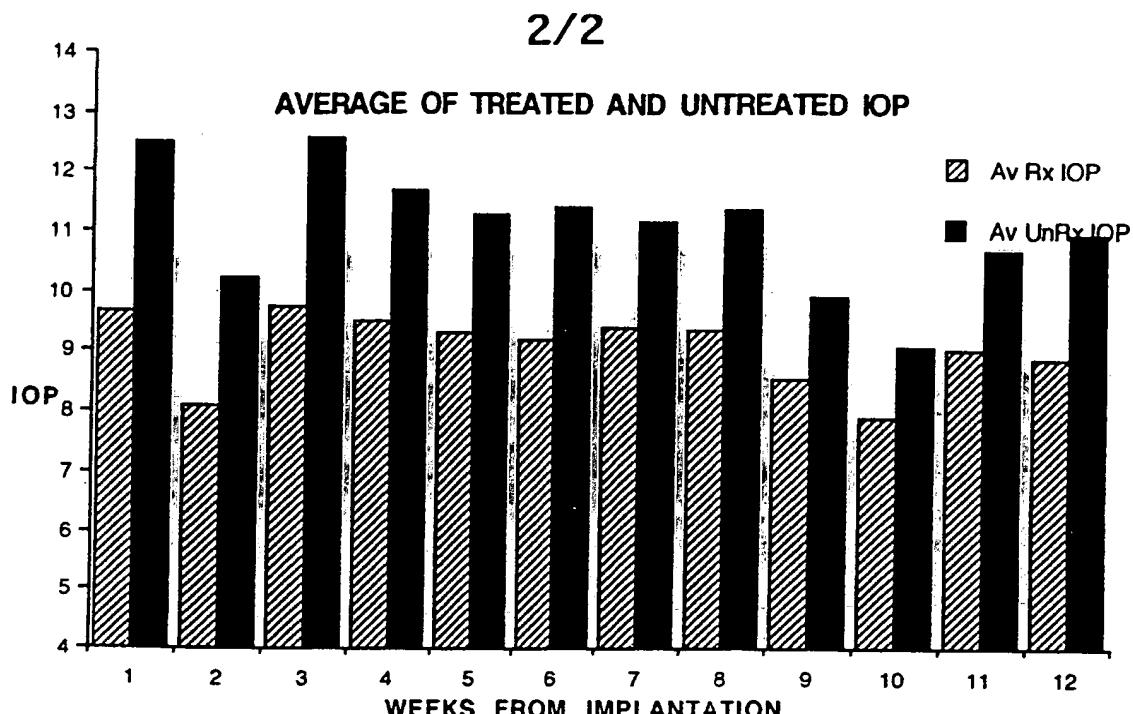
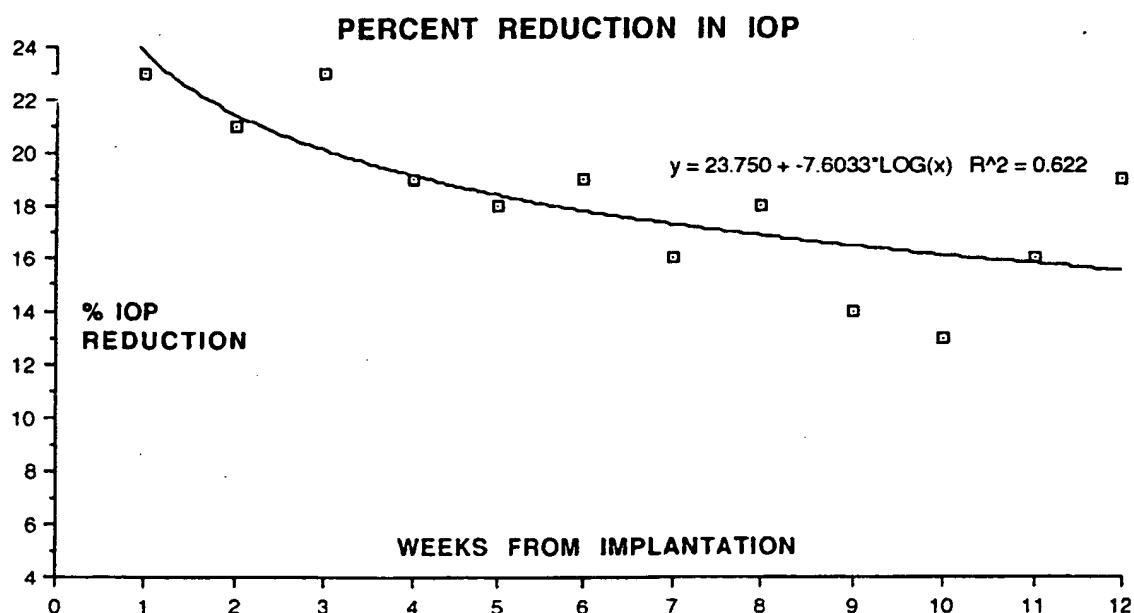


FIGURE 1B

**FIGURE 2A****FIGURE 2B**

INTERNATIONAL SEARCH REPORT

International application No.
PCT/AU 93/00656A. CLASSIFICATION OF SUBJECT MATTER
Int. Cl.⁵ A61F 9/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC A61F 9/00, A61M 27/00Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
AU: IPC as above, A61M 1/18Electronic data base consulted during the international search (name of data base, and where practicable, search terms used)
DERWENT: glaucoma or implant

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.
X Y	US,A, 4936825 (UNGERLEIDER) 26 June 1990 column 2 lines 29-45	1, 2, 5, 8, 14-17 3, 4, 6, 7, 9
X, Y	AU,B, 60248/86 (578164) (TERUMO KABUSHIKI KAISHA) 19 February 1987 (19.02.87) page 3a lines 21-24, page 4 lines 18-21	1, 2, 8, 9
Y	US,A, 4037604 (NEWKIRK) 26 July 1977 (26.07.77) column 3 lines 5-7	3, 4

 Further documents are listed
in the continuation of Box C. See patent family annex.

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 "O" document referring to an oral disclosure, use, exhibition or other means
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- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
 "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
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 "&" document member of the same patent family

Date of the actual completion of the international search
1 March 1994 (01.03.94)

Date of mailing of the international search report

09.03.94

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INTERNATIONAL SEARCH REPORTInternational application No.
PCT/AU 93/00656

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate of the relevant passages	Relevant to Claim No.
Y	WO,A, 91/12046 (ATOS MEDICAL AB) 22 August 1991 (22.08.91) page 7 lines 4-9	6, 7
A	WO,A, 91/07195 (SMITH) 30 May 1991 (30.05.91) page 6 lines 1-16, page 10 lines 13-20	1
A	GB,A, 2156684 (BINDER) 16 October 1985 (16.10.85) whole document	1
A	WO,A, 83/00420 (MENDEZ) 17 February 1983 (17.02.83) whole document	1

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

PCT/AU 93/00656

This Annex lists the known "A" publication level patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document Cited in Search Report				Patent Family Member			
AU	60248	CA US	1310455 4770852	CN US	86105092 5102590	EP JP	209465 62106770
WO	9107195	AU EP ZA	77866/91 454838 9009225	CA JP	2045178 4503767	CN US	1052253 4946436
WO	9112046	EP	515489	SE	9000491		
GB	2156684	DE US	3512440 4634418	FR US	2562419 4787885	JP	61033651
WO	8300420	CA	1187369	EP	84054	US	4428746
US	4037604						

END OF ANNEX